



Human Health Risk Assessment: Real World Application of Toxicological and Exposure Data

George M. Woodall, Jr., PhD



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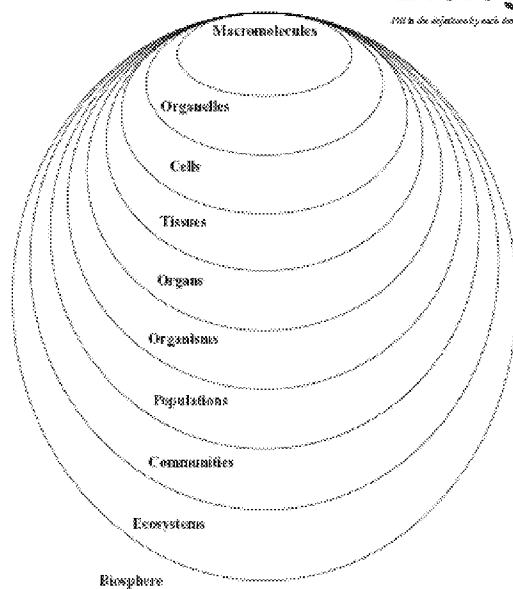
Office of Research and Development
National Center for Environmental Assessment

August 25, 2016

- Toxicology
 - * Hazard Identification
 - * Dose-Response
 - * Dose and Exposure Concentration
- Exposure
 - * Routes
 - * Fate and Transformation
 - * Scenarios
- Risk Characterization
 - * $\text{Dose Response Estimate} \times \text{Exposure Estimate} = \text{Hazard Estimate}$
 - * Weighing Benefits and Risks

Basic Principles of Toxicology

Still in the laboratory, each day



What is Toxicology

- Simple definition:
“the science of poisons”
- More Specific Definition:
“the study of the adverse effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects.”
[Society of Toxicology]



Classic Definition



"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy."
- Paracelsus (1493-1541)



Short-hand paraphrase:
The dose makes the poison

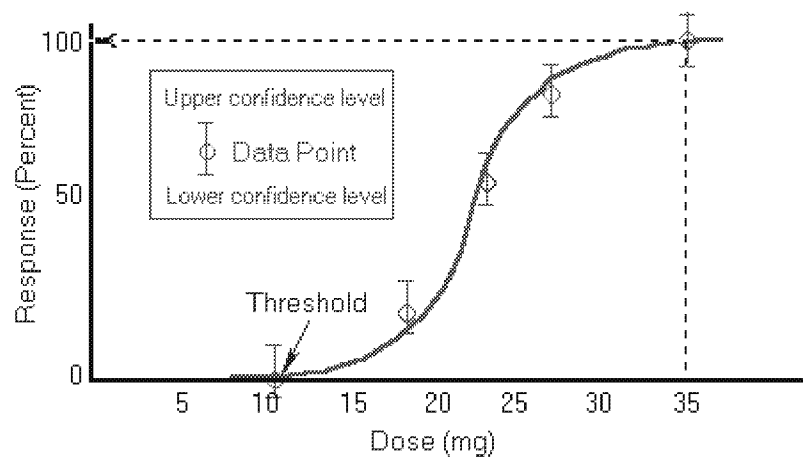
Examples of “Dose makes the poison (or remedy)”

Substance	Non-Toxic or Beneficial Dose	Toxic Dose	Lethal Dose
Alcohol <i>ETHANOL BLOOD LEVELS</i>	0.05 %	0.1 %	0.5 %
Carbon Monoxide <i>% HEMOGLOBIN BOUND</i>	< 10 %	20 - 30 %	> 60 %
Secobarbital (<i>sleep aid</i>) <i>BLOOD LEVELS</i>	0.1 mg/dL	0.7 mg/dL	> 1 mg/dL
Aspirin	0.65 gm (2 tablets)	9.75 gm (30 tablets)	34 gm (105 tablets)
Ibuprofen <i>E.G., ADVIL & MOTRIN</i>	400 mg (2 tablets)	1,400 mg (7 tablets)	12,000 mg (60 tablets)

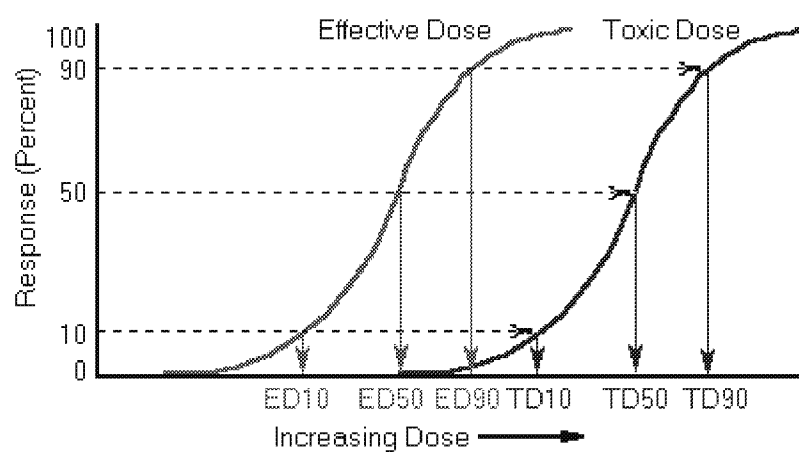
Principles of Clinical Toxicology (T. Gossel and J. Bricker, eds)

- Generally, the higher the dose, the greater the response.
- Dose-Response Key Terms:
 - Response: Establishes that the chemical has in fact caused the observed effects (good or bad)
 - Threshold: The lowest dose where an effect occurs
 - Slope: The rate at which the response builds up - the slope for the dose response

Dose-Response Curve

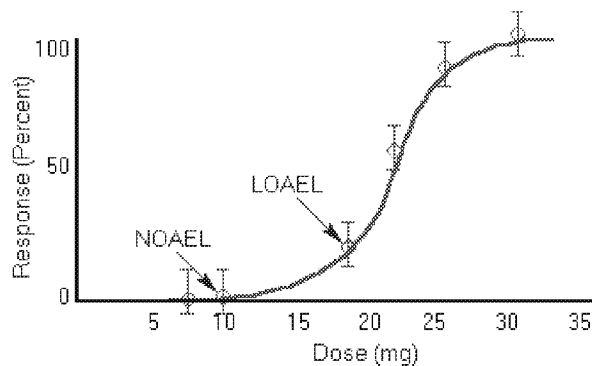


Effective vs. Toxic Doses



NOAEL and LOAEL

NOAEL	Highest data point at which there was not an observed toxic or adverse effect
LOAEL	Lowest data point at which there was an observed toxic or adverse effect

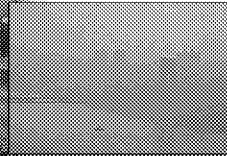
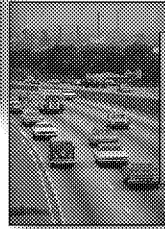


Risk Assessment Basic Principles

- **Hazard** is any source of potential damage, harm or adverse health effects on something or someone under certain conditions.
- **Risk** is the chance or probability that a person will be harmed or experience an adverse health effect if exposed to a hazard.

For a Risk to Occur...

1. A hazard must exist, and
2. Exposure must take place

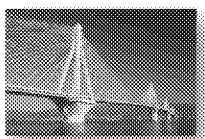


Question for the class?

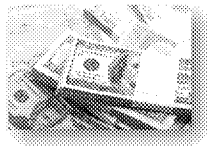
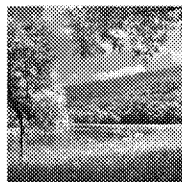
Can you think of any other hazard/risk scenarios? – they can be chemical, biological, physical, or natural.

“Risk Assessment” is Contextual

Engineering/
Structural

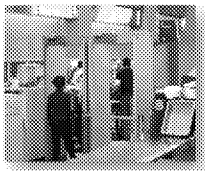


Ecological

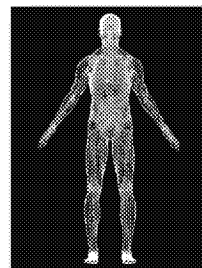


Financial/
Business

Security:
Vulnerability
and Threat



Human
Health



The field of RA can cover almost any aspect of life.

The term risk assessment is used in multiple contexts:

Engineering/structural

Financial/business

Security – vulnerability and threat assessment

Ecological

Human health

Physical injury

Radiation

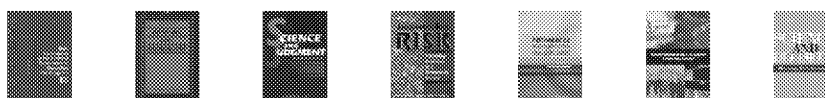
Microbial

Chemical

And because risk assessment is contextual, the definition can vary by context. The context of this course is human health risk assessment, primarily focused on chemical risk assessment, and so the definitions that we will discuss are presented from this perspective.

Brief History of Human Health Risk Assessment at EPA

- 1970: EPA established
- 1975: First EPA chemical assessment (vinyl chloride)
- National Research Council (NRC) publications on risk assessment
 - ✧ 1983: *Managing the Process* – the “Red Book”
 - ✧ 1989: *Improving Risk Communication*
 - ✧ 1994: *Science and Judgment* – the “Blue Book”
 - ✧ 1996: *Understanding Risk*
 - ✧ 2007: *Toxicity Testing in the 21st Century*
 - ✧ 2008: *Phthalates and Cumulative Risk Assessment*
 - ✧ 2009: *Science and Decisions* – the “Silver Book”



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Brief History of Human Health Risk Assessment

This is not a comprehensive history but rather an overview of some key events in the timeline of chemical, human health risk assessment as it relates to EPA.

EPA was established in 1970.

EPA completed its first risk assessment document in December 1975.

Reports of cases of liver cancer (many resulting in death) in workers at vinyl chloride facilities were reported in the media in the early 1970s. Some cases of angiosarcoma were reported in people who lived in the vicinity of facilities producing vinyl chloride. OSHA lowered permissible levels protecting workers, and EPA assessed the need to limit emissions of vinyl chloride into the air from these facilities.

EPA published the “Quantitative Risk Assessment for Community Exposure to Vinyl Chloride.”

Followed in 1976 by “Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens” published by EPA Administrator (these were not formal guidelines or policy, but were the beginnings of such guidelines)

As a scientific field, risk assessment continued to evolve – for example, the Society for Risk Analysis (SRA) published the first issue of Risk Analysis in 1981.

Then, between 1983 and 2009, the National Research Council (a part of the National Academy of Sciences) published several documents that are key to risk assessment.

The first book, published in 1983 was titled Risk Assessment in the Federal Government: Managing the Process. You may hear it referred to as the “Red Book” because of the color of its cover.

NRC was commissioned by Congress to prepare this set of recommendations

Book contains definitions and fundamental processes still in use today

This book introduced the risk assessment paradigm with its four traditional components:

Hazard Identification

Dose-response Assessment

Exposure Assessment

Risk Characterization

1994 - Science and Judgment in Risk Assessment, aka the “Blue Book”

Also commissioned by Congress (via Clean Air Act)

In part, a follow-up to the Red Book, but with specific emphasis on EPA’s scientific methods

2009 - Science and Decisions: Advancing Risk Assessment, aka the “Silver Book”

Discusses the planning and scoping principles of risk assessment along with stakeholder involvement, with EPA in mind

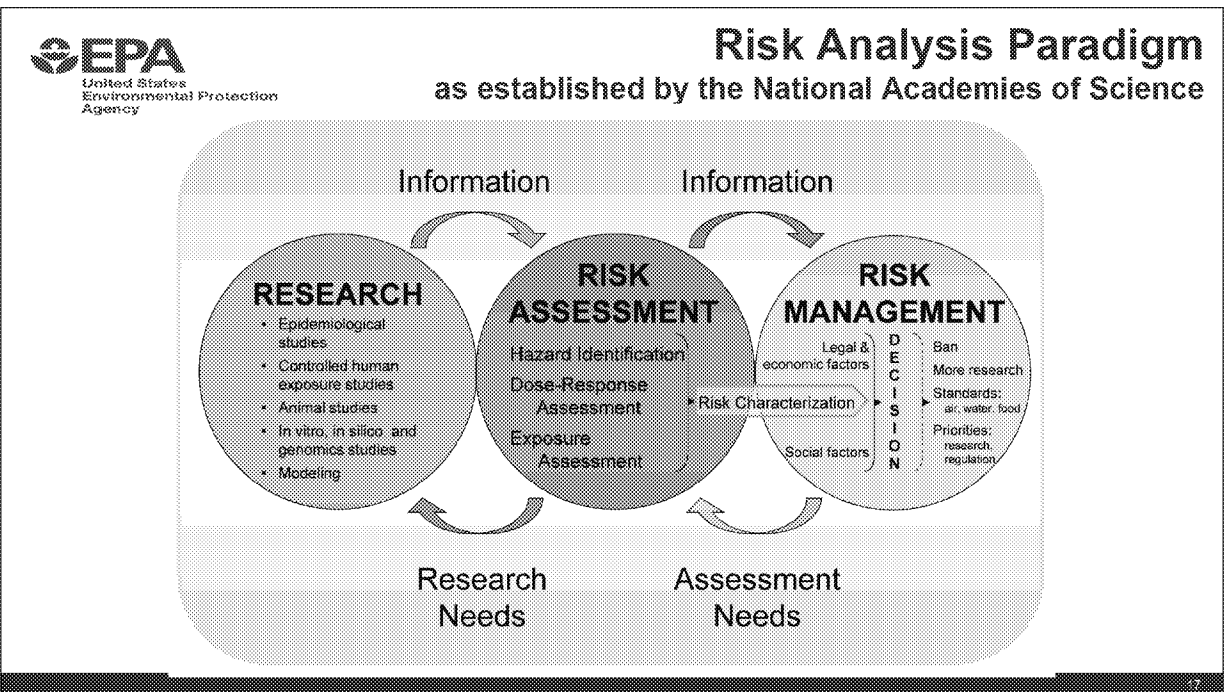
Other NRC publications on risk assessment include:

1989: Improving Risk Communication

1996: Understanding Risk

2007: Toxicity Testing in the 21st Century

2008: Phthalates and Cumulative Risk Assessment



are specific to human health RA.

Ecological RA has a slightly different outline and groups dose-response (effect) and exposure assessment. Risk assessment can be viewed as part of a broader "risk analysis" paradigm. The other two components are:

Research including epidemiology research, clinical studies, animal studies, in vitro, in vivo and modeling.

Risk management which covers regulatory (or other) decision-making.

Some people also include risk communication which covers effectively communicating the results of risk assessment and the policy implications of risk management decisions.

This course is focused on risk assessment, which is primarily concerned with scientific evaluation

For IRIS chemical managers, particular emphasis on hazard identification and dose-response assessment.

Within the risk assessment circle, the four basic components of risk assessment are listed (according to the 1983 NRC red book).

Hazard Identification

Dose-response Assessment

Exposure Assessment

Risk Characterization

Many groups who have defined risk assessment include these 4 components (or some variation) in the definition. (Did the class come up with these? If so, acknowledge.)

Although the 3 circles are more general than just human health risk assessment, the 4 components of risk assessment base."

Two other recent additions to the risk assessment paradigm are

Stakeholder involvement – emphasis on stakeholder involvement through all phases of risk assessment. This includes internal and external stakeholders, and

Problem formulation and scoping – emphasizes thinking through the possible risk management options before beginning the risk assessment. This is a necessary step in order to decide what information should be collected during the actual risk assessment.

Risk Assessment Definitions

Hazard
Identification

Dose-response
Assessment

Exposure
Assessment

Risk
Characterization

Risk assessment is the evaluation of scientific information on:

- * the hazardous properties of environmental agents,
- * the dose-response relationship, and
- * the extent of human exposure to those agents.

The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree.

From EPA's Glossary of IRIS Terms

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A second, expanded definition of risk assessment can be found in EPA's Glossary of IRIS Terms. We're presenting this definition because IRIS is the focus of many of the courses to come in this series.

IRIS is EPA's Integrated Risk Information System; it is an important data base of toxicity information that NCEA developed and maintains.

This definition is based on the 4 components of the risk assessment paradigm developed by the National Research Council or NRC.

Risk assessment, in terms of human health, is the evaluation of scientific information on:

the hazardous properties of environmental agents (This is hazard identification, and IRIS assessments include hazard identification.),

the dose-response relationship (This is dose-response assessment and is also included in IRIS assessments.), and

the extent of human exposure to those agents (This is exposure assessment.).

The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (This is the risk characterization component of the National Research Council's paradigm). Risk characterization synthesizes the information collected and evaluated in the other three steps.

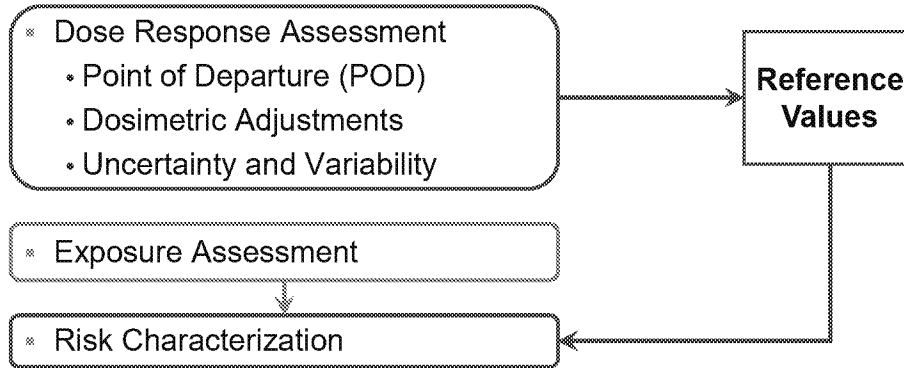
An analogous and similar (but not identical) definition exists for ecological risk assessment.

There is variation among federal agencies regarding the conduct of RA, but the overarching frameworks that Agencies use are based on the NRC paradigm. Details can differ based on statutory requirements and history of practice within the agency.

Dose-Response Assessment and Reference Values

Relevance of Reference Values

- Risk Analysis Paradigm
 - Hazard ID

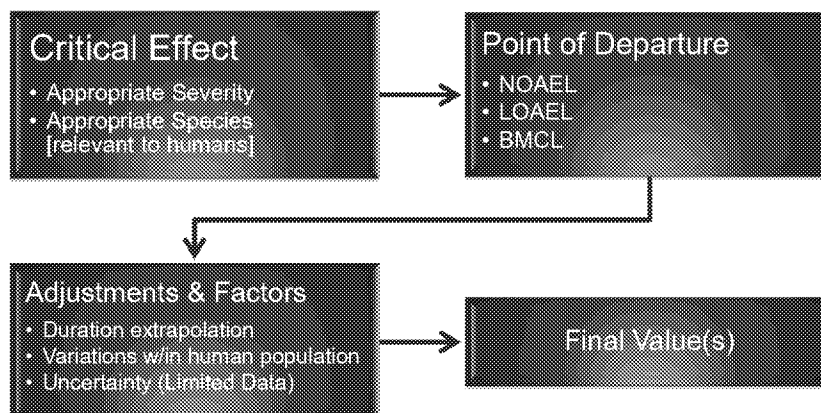


Reference Value Definitions

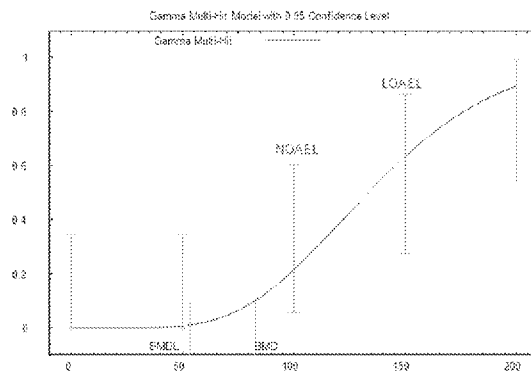
- **Reference Value** – a general term for all values for a specific agent designed to specify a level for adverse health effects.
 - * Agents may be chemical, microbial, or radiation
 - * Health effects can be cancer or noncancer
- **Synonyms**
 - * Toxicity Values
 - * Health Effect Values
 - * Health Benchmarks
- **Examples of Values**

Reference Values in IRIS by Route	Oral	Inhalation
Cancer	Slope Factor	Unit Risk
Noncancer	Reference Dose (RfD)	Reference Concentration (RfC)

Typical Reference Value Derivation [Human Inhalation Data]

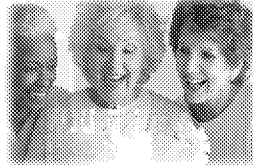


- **Point of Departure (POD):** Dose-response point that marks the beginning of a low-dose extrapolation
- POD can be a LOAEL, a NOAEL, or a BMDL

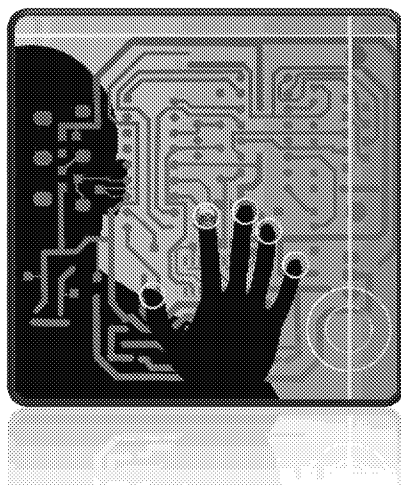


Definition of Variability

- Variability refers to true heterogeneity or diversity
 - * Inherent property of a population
 - * Can be characterized with more data, but cannot be reduced or eliminated
- Cannot be reduced or altered, only described



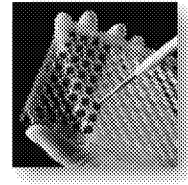
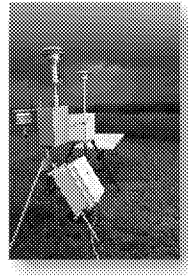
Sources of Variability



- Inter-individual variability
 - ✧ Differences among individuals in a population
- Intra-individual variability
 - ✧ Differences for one individual over time

Definition of Uncertainty

- Uncertainty refers to a lack of knowledge arising from...
 - ✧ Incomplete data
 - ✧ Incomplete understanding of processes
- Approximations and assumptions can be used to account for incomplete data/understanding
- Uncertainty often reduced by collecting more and better data



Sources of Uncertainty

- Data, from a wide range of disciplines
- Limited data
- Scientific assumptions
- Science policy choices
 - ✧ Choices are made to bridge gaps in knowledge when a decision or action is required

Uncertainty Factors in IRIS Noncancer Assessments

Identify or Derive POD

- Select study; Extract D-R data
- Dosimetric Adjustments

Select Uncertainty Factors

Derive Reference Dose or Reference Concentration

$$\text{Reference Value} = \frac{\text{POD}}{\text{UF}}$$

What are the Uncertainty Factors?

UF_H – intraspecies uncertainty

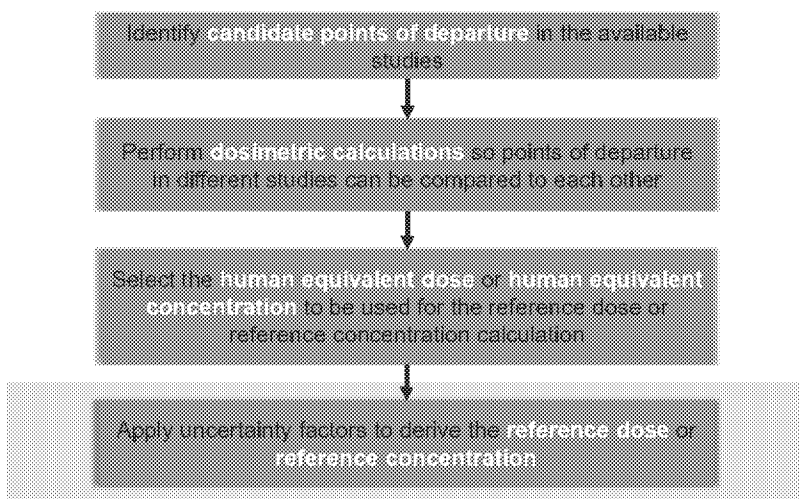
UF_A – interspecies uncertainty

UF_S – subchronic to chronic extrapolation

UF_L – LOAEL to NOAEL extrapolation

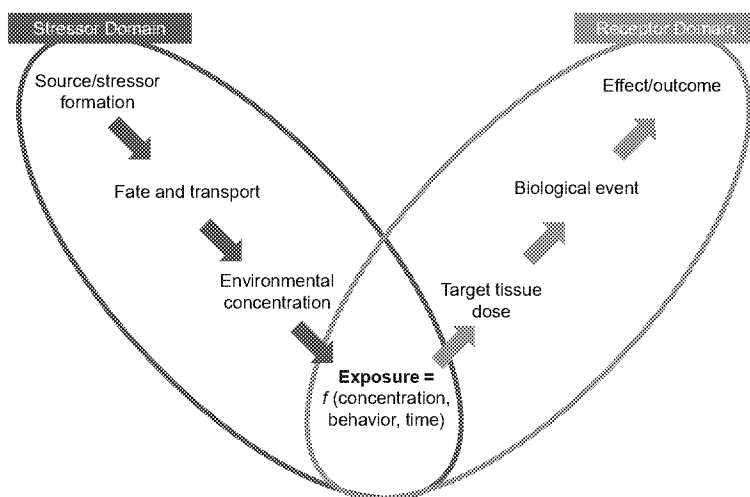
UF_D – database deficiencies

Dose-Response Assessment: Reference Values

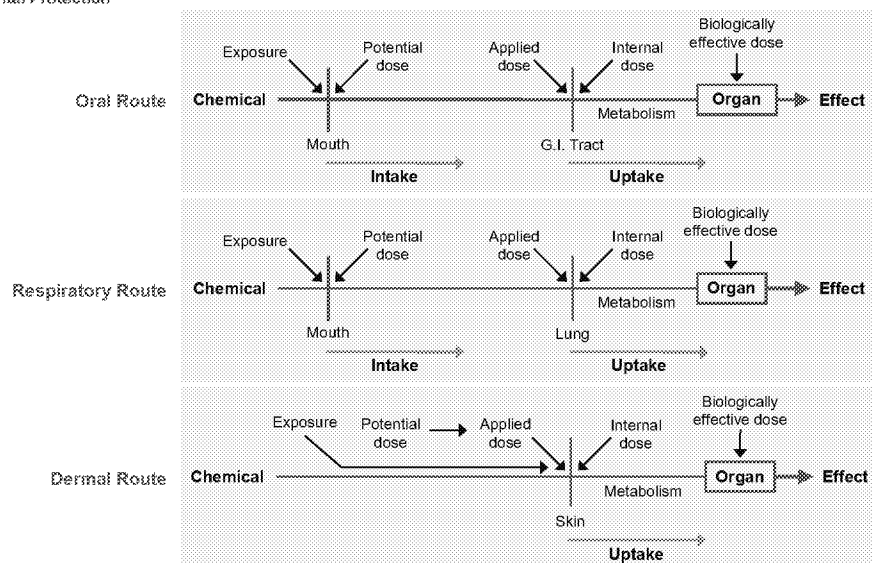


General Concepts of Exposure Assessment

Source-to-Effect Continuum



Dose Illustrated



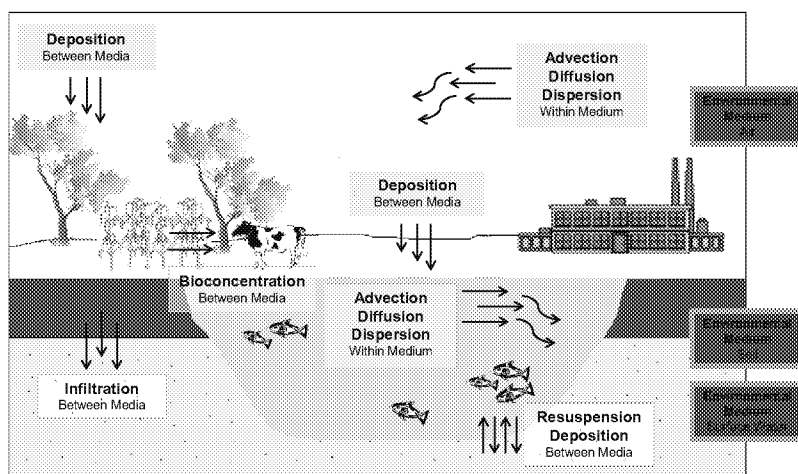
Individual- versus Population-Level Assessments

- Exposure assessment usually conducted for populations or groups
- Exposure factors, or characteristics of the population, important to estimate exposure and risk:
 - ✧ Food and water intake
 - ✧ Population behaviors
 - ✧ Inhalation rates
 - ✧ Other factors relevant to scenario
- Variability and uncertainty in exposure factors

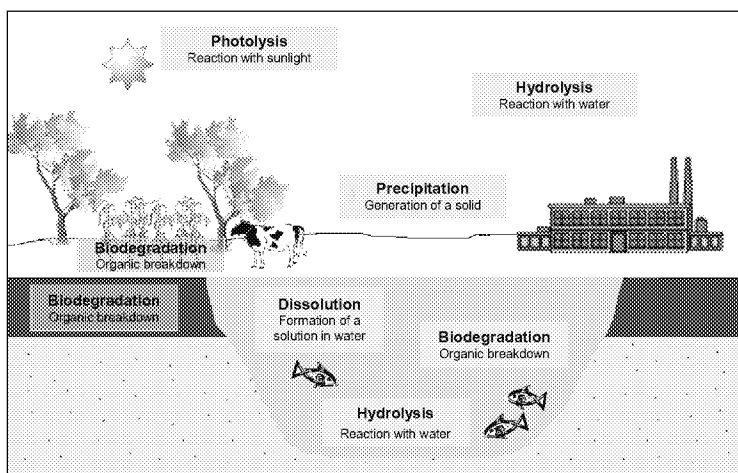


Fate and Transport

Transport: Movement Within and Between Environmental Media



Transformation: Chemical Changes within a Medium

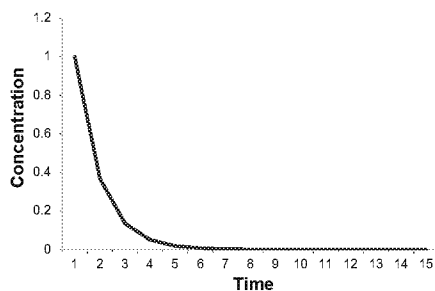


First-order Decay

$$C_t = C_0 \exp(-kt)$$

Where:

- * C_t = concentration at time t
- * C_0 = concentration at time 0
- * k = first-order decay rate constant (expressed in units of $1/t$)
- * t = time



Half-life ($t_{1/2}$): Time required for original concentration to be reduced by half
Rate constant (k) = $\ln(2)/t_{1/2}$

This slide is only provided to illustrate that there is much more depth to these considerations than time allows to discuss.

- Influences on fate and transport
 - ✧ Chemical, source, environmental characteristics
- Important fate processes
 - ✧ Intraphase: transport, diffusion, dispersion
 - ✧ Interphase partitioning
- Transformations
 - ✧ Degradation, conversion, other processes for organic, inorganic chemicals
 - ✧ First-order decay

Developing Exposure Scenarios and Calculating Dose

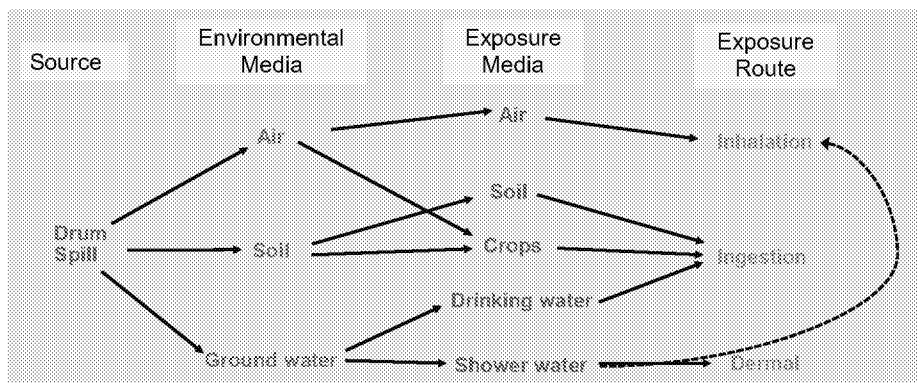
What is an Exposure Scenario?

- An **exposure scenario** is a set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposure.

Source: EPA's Example Exposure Scenarios Guide (2004)

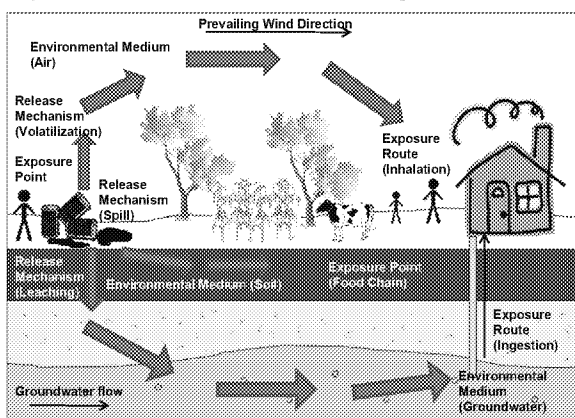
Exposure Pathway and Exposure Route

- **Exposure pathway:** the physical course a chemical takes from the source of the chemical to the exposed individual
- **Exposure route:** the way a chemical enters an individual upon contact



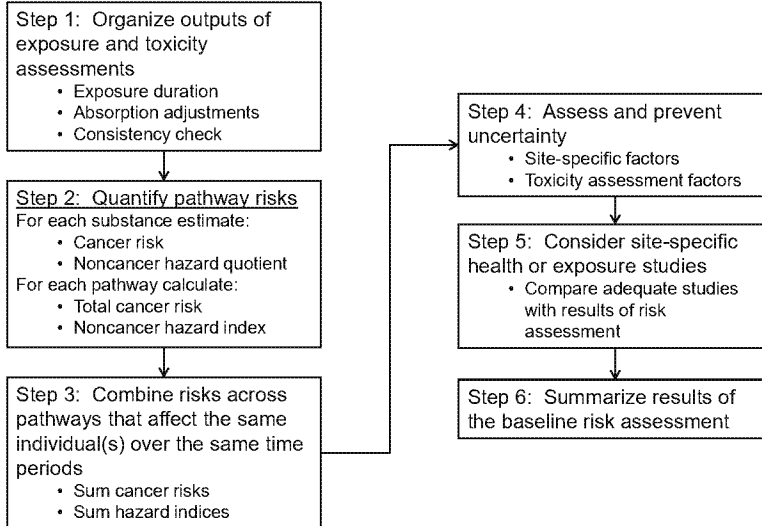
Putting It All Together

- **Exposure setting:** drum spill in uncontained outdoor setting inhabited by humans and wildlife
- **Exposure pathways:** air, soil, water
- **Exposure media:** air, soil, water, plants, animals
- **Exposure routes:** inhalation, ingestion, dermal contact
- **Chemical of concern:** physical chemical properties, amount and location of release, concentration
- **Exposed population:** humans (adults and children) and wildlife



Risk Characterization

Steps in Risk Characterization



This slide is only provided to illustrate that there is much more depth to these considerations than time allows to discuss.

Information Needed for Risk Characterization

- Toxicity Info
 - ✧ Cancer
 - Slope factors
 - Weight of Evidence descriptor
 - ✧ Noncancer
 - Reference Values (e.g., RfD/RfC)
 - Critical effects
 - Uncertainty info
- Intake estimates
- Exposure info
 - ✧ Frequency & duration info
 - ✧ Absorption assumptions
 - ✧ Uncertainty info
- Completed exposure pathways

Usually cancer risk drives the cleanup process b/c it is a very conservative estimate and generally contributes most to overall risk

Calculation for Noncarcinogens

- Non-cancer effects are assessed by hazard quotients (HQ)
- For oral exposures:

$$HQ = \frac{\text{Intake}}{\text{RfD}}$$

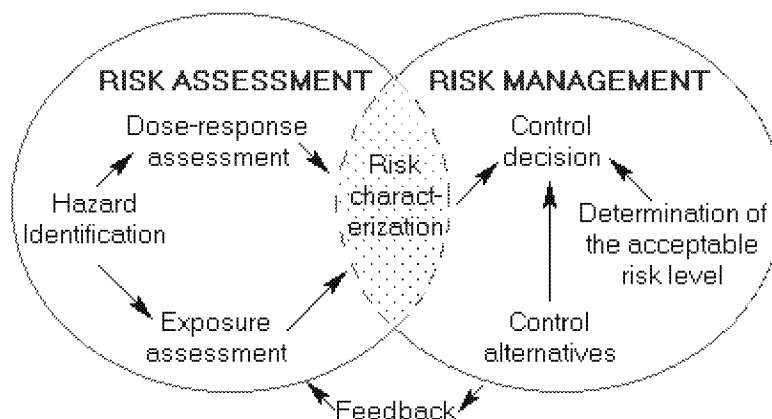
- For inhalation exposures:

$$HQ = \frac{\text{Exposure Concentration}}{\text{RfC}}$$

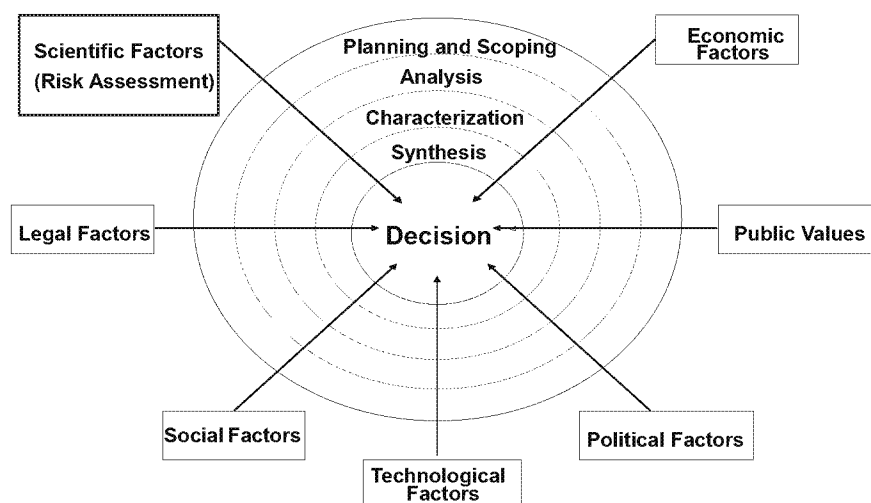
Note: for oral exposures, intake and RfD both have units of mg/kg-day and for inhalation exposures, intake and RfC both have units of mg/m³, so HQ is a unitless ratio in both instances

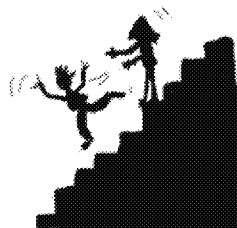
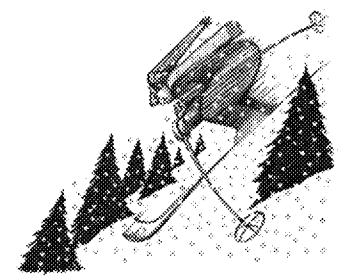
Risk Management: Where Science and Policy Meet

Flow of Information for Making Risk Decisions



Risk Management Decision Framework





[Video Clip \(Courtesy of University of Michigan
Risk Science Center - 1:54\)](#)

Case Study: Weighing Risk and Benefits of Water Chlorination

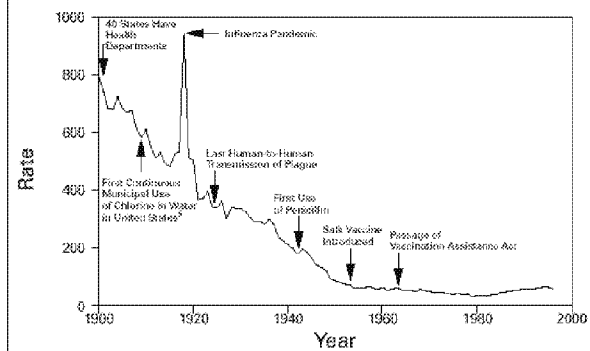
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History of Drinking Water Treatment

- American drinking water supplies are among the safest in the world.
- Disinfection of water has played a critical role in improving drinking water quality in the United States.
- Example: Typhoid fever in the US
 - 1900: 100 cases per 100,000 people.
 - 1920: 33.8 cases per 100,000 people.
 - 2006: 0.1 cases per 100,000 people (only 353 cases) with approximately 75% occurring among international travelers

FIGURE 1. Crude death rate* for infectious diseases — United States, 1900–1996[†]



*Per 100,000 population per year.

[†]Adapted from Armstrong GL, Conn LA, Finner RV. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999;281:31-6.

[‡]American Water Works Association. Water disinfection principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

The benefits of chlorination are:

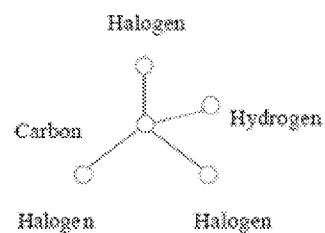
- Proven reduction of most bacteria and viruses in water
- Long-lasting protection against recontamination
- Ease-of-use and acceptability
- Proven reduction of diarrheal disease incidence
- Scalability and low cost

The drawbacks of chlorination are:

- Potential taste and odor objections
- Potential long-term effects of chlorination by-products

- Disinfection By-Products
 - ⌘ Created by reaction of chlorine with organic matter in water
 - ⌘ Trihalomethanes = typical by-product, but there are others
 - ⌘ Have been associated with increases in certain types of cancer (esp. liver, kidney, colon)

Trihalomethanes



- Four major trihalomethanes
 - ⌘ Chloroform - CHCl_3
 - ⌘ Bromodichloromethane (BDCM) - CHCl_2Br
 - ⌘ Dibromochloromethane (DBCM) - CHClBr_2
 - ⌘ Bromoform - CHBr_3

- Pretreatment of water to remove organic matter
- Using only the amount of chlorine needed to keep water free of disease agents
- Using alternative disinfection agents
 - UV radiation – does not persist
 - Ozonation – does not persist; hazards for operators of water systems

Final Thoughts and Additional Resources

- Water chlorination
 - Drinking Water Chlorination Turns 100 (ACC):
<https://www.youtube.com/watch?v=op8sGKTINzA>
 - History of Drinking Water Treatment (CDC):
<http://www.cdc.gov/healthywater/drinking/history.html>
 - Chlorination by-products (EPA):
<http://water.epa.gov/drink/contaminants/basicinformation/disinfectionbyproducts.cfm>
- Toxicology
 - ToxTutor (Nat'l Library of Medicine): <http://sis.nlm.nih.gov/enviro/toxtutor.html>
 - ToxLearn (NLM & Society of Toxicology): <http://toxlearn.nlm.nih.gov/index.html>
- Risk
 - Risk Bites Archive (University of Michigan Risk Science Center):
<http://www.youtube.com/channel/UC8oxdTK0M0HdZB3gyJNiEtw>
- Green Chemistry (<http://www2.epa.gov/green-chemistry>)
- Sustainability (<http://www.epa.gov/sustainability/index.htm>)

Thank you for your attention

*It is better to know some of the
questions than all of the answers.*

James Thurber (1894 - 1961)

*The most erroneous stories are those we think we know
best - and therefore never scrutinize or question.*

Stephen Jay Gould (1941 - 2002)